PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/045 — A1

(11) International Publication Number: WO 99/26612

(43) International Publication Date: 3 June 1999 (03.06.99)

(21) International Application Number: PCT/US98/24803

(22) International Filing Date: 20 November 1998 (20.11.98)

(30) Priority Data:

60/066,353	21 November 1997 (21.11.97)	US
60/068,085	19 December 1997 (19.12.97)	US

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BENDER, Paul, E. [US/US]; 504 Lilac Lane, Cherry Hill, NJ 08003 (US). CHRISTENSEN, Siegfried, Benjamin, IV [US/US]; Rivers Edge, 2301 Cherry Street #4–M, Philadelphia, PA 19103 (US). LEE, Jonathan, A. [US/US]; 1706A Handball Lane, Indianapolis, IN 46260 (US).

(74) Agents: SIMON, Soma, G. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406–0939 (US).

(54) Title: NOVEL CANNABINOID RECEPTOR MODULATORS

(57) Abstract

Cannabinoid receptor modulators and methods of using them are provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NOVEL CANNABINOID RECEPTOR MODULATORS

FIELD OF THE INVENTION

The present invention relates to the use of dialkyl phenol derivatives, and pharmaceutical compositions containing these compounds as cannabinoid peripheral receptor agonists.

Cannabinoids are a specific class of psychoactive compounds present in Indian cannabis (*Cannabis sativa*), including about sixty different molecules, the most representative being cannabinol, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of cannabis dates back to the ancient dynasties of China, where, 5,000 years ago, cannabis was used for the treatment of asthma, migraine and some gynaecological disorders. These uses later became so established that, around 1850, cannabis extracts were included in the US Pharmacopaeia and remained there until 1947.

Cannabinoids are known to cause different effects on various systems and/or organs, the most important being on the central nervous system and on the cardiovascular system. These effects include alterations in memory and cognition, euphoria, and sedation. Cannabinoids also increase heart rate and vary systemic arterial pressure. Peripheral effects related to bronchial constriction, immunomodulation, and inflammation have also been observed. The capability of cannabinoids to reduce intraocular pressure and to affect respiratory and endocrine systems is also well documented. See e.g. L.E. Hollister, Health Aspects of Cannabis, Pharmacological Reviews, Vol. 38, pp. 1-20, (1986). More recently, it was found that cannabinoids suppress the cellular and humoral immune response and have antiinflammatory properties. Wirth et al., Antiinflammatory Properties of Cannabichrome, Life Science, Vol. 26, pp. 1991-1995, (1980).

The initial demonstration of the existence of a cannabinoid receptor by radioreceptor binding occurred in 1988 followed by the cloning and characterization of the central acting receptor and peripheral receptor in 1990 and 1993 respectively.

Matsuda and collaborators identified and cloned a cannabinoid receptor belonging to the G-protein-coupled family of receptors, wherein CB1 is coupled to G1 to inhibit adenilate cyclase activity and to a partussis-sensitive G protein to regulate Ca^{2+} currents. The receptor is question was found to be mainly located in the brain, in neural cell lines, and, only to a lesser extent, at a peripheral level. In view of its location, it was called the Central Receptor ("CB1"). See Matsuda et al., "Structure of a Cannabinoid Receptor and

Functional Expression of the Cloned cDNA," Nature, Vol. 346, pp. 561-564 (1990). The discovery of this receptor led one to assume the existence of a specified endogenous ligand.

Subsequent research led to the isolation of a substance from the pig brain that was able to exert an antagonist action, i.e. bind to the cannabinoid central receptor in a competitive way. The substance was identified by structural investigation and by comparison with the synthetic product. It was found to be an amidic derivative of arachidonic acid, more particularly arachidonylethanolamide, later called anandamide. The pharmacological characterization of the molecule provided evidence that anandamide possessed a profile of activity which was similar to, though less potent than, delta-9-THC (tetrahydrocannabinol with a double bond in position 9), and was capable of mimicking the psychoactive effects thereof. This evidence led to the conclusion that anandamide was the endogenous ligand of the cannabinoid central receptor. See Felder, et el., "Anandamide, an Endogenous Cannabimimetic Eicosanoid, Binds to the Cloned Human Cannabinoid Receptor and Stimulates Receptor-mediated Signal Transduction," PNAS, Vol. 90, pp. 7656-7660 (1994).

Subsequent research led to the individuation of substances binding to CB1 receptor; these substances, grouped together into a class of amidic compounds, were denominated anadamides by the authors. Hanus, et el., "Two New Unsaturated Fatty Acids Ethanolamides in the Brain that Bind to the Cannabinoid Receptor," J. Med. Chem., Vol. 36, pp. 3032-3034, (1993).

The discovery that the ethanolamide of arachidonic acid, but not the ethanolamide of other acids which are biologically important and already endogenously present at the cerebral level (such as palmitic acid), is capable of functionally activating CB1 central receptor, brought about the subsequent identification of other amides of ethanolamine with highly unsaturated fatty acids which have an affinity to the CB1 receptor.

Its unique distribution led to the assumption of the existence of differentiated receptor sites. A second receptor for cannabinoids was cloned. This was named the Peripheral Receptor (CX5 or CB2). This receptor was identified in the spleen and macrophages/monocytes while being absent at the central level. It is assumed that this receptor mediates the non psychoactive effects of the cannabinoids. See Munro et el., "Molecular Characterization of a Peripheral Receptor for Cannabinoids," Nature, Vol. 365, pp. 61-65 (1993). In this connection there is evidence of the capacity of delta-9-THC to induce immunosuppressive effects. Recent experimental studies have demonstrated that delta-9-THC is capable of influencing the function of macrophage. Exposure to delta-9-

THC lowers the cytolytic action of activated macrophages, measured as synthesis, release and cytotoxicity of TNF-alpha. Because the macrophages release various molecules having a cytolytic potential, other than TNF-alpha, it is considered that they can represent a target for delta-9-THC. See Fischer-Stenger et el., "Delta9-tetrahydrocannabinol Inhibition of Tumor Necrosis Factor-alpha: Suppression of Post-translational Events," J. Pet., Vol. 267, Pp. 1558-1565 (1993).

The foregoing indications and the preferential massive localization of the CB2 receptor in the immuno system confirms that this receptor plays a specific role in mediating the immune and antiinflammatory response to stimuli of different nature, including bacterial and viral ones.

Research efforts also indicate that anandamide, the endogenous ligand for the CB1 central receptor, is capable of binding to the CB2 receptor with an affinity which is 30 fold lower to that of the central receptor. This probably implies the existence of a separate endogenous ligand up to now still unknown. Iversen, "Medical Uses of Marijuana?' Nature, Vol. 365, pp. 12-13 (1993).

As already mentioned, the therapeutic uses of cannabinoids as analgesics, antiemetics, anticonvulsives, antispastics, antiglaucoma and, more recently, antiinflammatory agents, is limited by the undesirable side effects and by the possibility of addiction and pharmacological tolerance.

The foregoing research advances have provided the impetus to investigate the role of the cannabinoid receptors in immunomodulation, inflammation, osteoporosis, cardiovascular, neurological, renal and other disease conditions. Cannabinoid receptor modulators thus offer a unique approach toward the pharmacotherapy of immunosuppression, neurological inflammation, arthritis, osteoporosis, renal ischemia, hematopoiesis, analgesia, neuropathic pain, pathologies related to improper small blood vessel vasodilation and other pathophysiological conditions.

Therefore novel, structurally distinct cannabinoid receptor agonists may find therapeutic uses as analgesics, antiemetics, anticonvulsives, antispastics, antiglaucoma, immunomodulators and antiinflammatory agents and not be limited by the undesirable side effects and by the possibility of addiction.

Recently, some compounds have been prepared, capable of acting as agonists on both the cannabinoid receptors. For example, use of derivatives of dihydroxypyrrole-(1,2, 3-d,e)-1,4-benzoxazine in the treatment of glaucoma and the use of derivatives of 1,

5-diphenyl-pyrazole as immunomodultors or psychotropic agents in the treatment of various neuropathologies, migraine, epilepsy, glaucoma, etc are known. See U.S. Patent No. 5,112,820 and EP 576357, respectively.

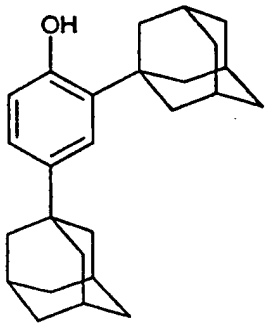
SUMMARY OF THE INVENTION

The present invention involves 2,4-bis-(1-adamantyl)phenol and its use as a cannabinoid receptor agonist, useful in the treatment of a variety of diseases associated with cardiovascular, renal, neurological and immune disorders, including but not limited to immunologically-mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple schlerosis, diabetis and thyroiditis; bone conditions including but not limited to ankylosing spondylitis, gout, arthritis associated with gout, osteoarthritis and osteoporosis.

The present invention further provides methods for agonizing cannabinoid receptors in an animal, including humans, which comprises administering to a subject in need of treatment an effective amount of the present compound.

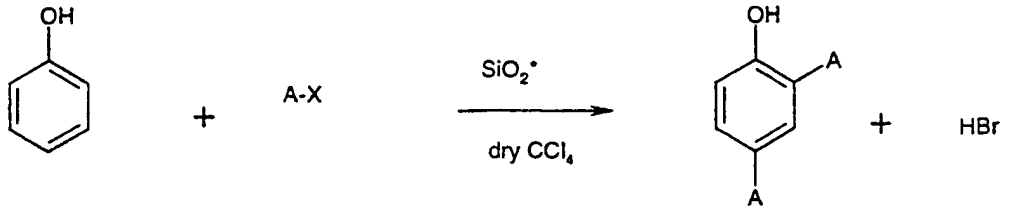
DETAILED DESCRIPTION OF THE INVENTION

The compound useful in the present methods is 2,4-bis-(1-adamantyl)phenol:



Also included in the present invention are pharmaceutically acceptable salt complexes. Preferred are the ethylene diamine, sodium, potassium and calcium salts.

The present compound can be prepared by the using the strategies provided hereinbelow as well as the specific example cited.



1 2 Formula I

wherein A-X represents 1-adamantyl halide, wherein the halide is chloride, iodide or preferably bromide.

Scheme 1

Formula I compounds are prepared by the process of Scheme 1 which comprises: heating a 1-adamantyl halide of Formula 2 with a phenol of formula 1 at 50 to 150 °C in a dry suitable solvent such as carbon tetrachloride, or dichloroethane for 10 to 48 h in the presence of a Lewis acid catalyst such as silica (activated by heating between 100 and 250 °C under vacuum for 1 to 24 h.).

In order to use the present compound or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

In addition to the conditions listed hereinabove, the present compound is useful for the treatment of diseases including but not limited to immunologically-mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple schlerosis, diabetis and thyroiditis. In addition, the present compound modulates bone formation/resorption and is useful in the treatment of conditions including but not limited to ankylosing spondylitis, gout, arthritis associated with gout, osteoarthritis and osteoporosis.

The present compound and its pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, dermally, transdermally, rectally, via inhalation or via buccal administration.

Composition of the present compound and its pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for

preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil. for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises the present compound or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of Formula(I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of the present compound.

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of the present compound or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of the compound or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when the present compound is administered in accordance with the present invention.

The biological activity of the present compound is demonstrated by the following test:

CANNABINOID RECEPTOR BINDING ASSAY

Rat CB1 membranes (rCB1) are made from homogenized cerebellum, recombinant human CB1 membranes (hCB1) are obtained from Receptor Biology Inc. (Baltimore, MD), and human CB2 membranes (hCB2) are made from a polyclonal HEK 293 cell line stably expressing the human CB2 receptor. The assay buffer comprises 50 mM Tris(pH7.4), 5mM MgCl2, 2.5 mM EDTA and 5 mg/ml Bovine Serium Albumin Fraction V fatty acid-free(Cal Biochem). Unless otherwise noted, all chemicals are from Sigma. Tritiated 5-(1,1-dimethylheptyl)-2-(5-hydroxypropyl)cyclohexyl)-1 alpha, 2beta, 5 alpha)-phenol([^{3}H]-CP55,940,103.4 Ci/mmol, 1mCi/ml) is purchased from DuPont NEN. Test compounds are made by Medicinal Chemistry SmithKline Beecham Pharmacuticals and are dissolved in DMSO.

The ligand binding mixture contains 1.3-1.8nM [^{3}H]-CP55,940, 5 ul of each test compound in a total reaction volume of 150 ul of assay buffer and either 50 ug/ml of rCB1, 25 ug/ml hCB1, or 20 ug/ml hCB2 membranes. The final concentrations of compounds range from 1.00E-4 to 1.00E-10M; and the final DMSO concentration is 3.3%. The ligand binding mixtures are incubated in 96 deep well polypropylene microtiter plates for one hour at 30° C and terminated by rapid filtration (Brandel 96-well cell harvester) over GF/B filters treated with wash buffer(50 mM Tris, 0.5 mg/ml fatty acid-free BSA, pH7.4), and followed by five washes with 3 ml ice-cold buffer. The filters are air-dried and [^{3}H]-CP55,940 bound radioactivity is determined by liquid scintillation counting. Non-specific binding is determined in the presence of 1 uM CP55,940. The binding data is analyzed with

the program GraphPad Prism. K_i values ranging from 1 nM to 10 uM are obtained for the compounds of the present invention.

cAMP PRODUCTION IN HEK293/CB2 CELLS METHODOLOGY

To confirm agonist activity, the following test is conducted.

Polyclonal HEK293 cells stably expressing human CB2 receptor are maintained in EMEM media supplemented with Earl's salts, L-glutamine, 10% FBS, and 0.5mg/ml G418 sulfate. 200 uL of cell suspension (25,000-50,000 cells/well) are added to a 96 well plate pre-treated with dilute Matrigel (Collaborative Biomedical Products: diluted 1/50 with PBS and treated for 1 hr at room temperature) and incubated at 37 °C for three days in a 5% CO_2 incubator.

Growth media is removed from the assay plate and each well is rinsed with 200 uL of cAMP assay buffer (EMEM media supplemented with Earl's salts, L-glutamine, 20mM Hepes, pH 7.4, 0.1mM $MgCl_2$ and 2mg/ml BSA Fraction V) and blotted dry. 50 uL of assay buffer are added to each well, followed by 100 uL of 250 uM Zardaverine (a PDE 3-4 inhibitor diluted in assay buffer with 0.25% DMSO) and 50 uL of the test compound (diluted in assay buffer containing 20mg/ml BSA and 1% DMSO). The cells are then incubated with compounds at room temperature for 30 minutes. To initiate cAMP production, 50 uL of 50 uM Forskolin (Calbiochem 344270 in assay buffer with 0.1% DMSO) is added and incubated for 15 minutes in a 37 °C incubator. The reaction is terminated by addition of 60uL 0.2N HCl and 0.2mM $CaCl_2$ and stored in a -80 °C freezer until cAMP determination.

For cAMP determinations 200 uL of cell lysate is transferred to a 96 well round-bottom plate and 40 uL of 0.1N NaOH and 0.1mM CaCl2 is added to neutralize the lysate. Following centrifugation at 2400 rpm for 5 minutes, 20-50µL of supernatant is assayed for cAMP using the Amersham EIA kit (RPN 225: unacetylated protocol). Using this procedure, forskolin stimulated cAMP levels range from 0.5-1.5 pmole per assay well and 5-15 pmole per original culture.

The following example is illustrative but not limiting of the embodiments of the present invention.

EXAMPLE 1

Preparation of 2,4-bis-(1-Adamantyl)phenol.

Activated silica was prepared by heating Silica Gel 60 (EM Industries) in a flask under high vacuum at 180 °C for 12 h. and was stored under an argon atmosphere. A stirred

suspension of activated silica (1.5g) 1-adamantyl bromide (2.6 g, 12 mmol) and anhydrous phenol (188 mg, 2 mmol), in dry carbon tetrachloride was heated at reflux under an argon atmosphere for 18 h. Another portion of activated silica (0.43 g) was added and the mixture refluxed another 18 h. The resulting mixture was filtered on a Buchner funnel, the solid rinsed with methylene chloride, and the chilled filtrate neutralized with chilled sodium carbonate solution. The organic phase was dried over anhydrous sodium carbonate, filtered, and concentrated *in vacuo*. The residue was chromatographed (silica gel; chloroform: cyclohexane; 1:2), and the pure fractions combined and concentrated to afford the titled compound as a white solid (29% yield, 210 mg), mp 202-203 °C.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

EXAMPLE 2

Inhalant Formulation

The present compound is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

EXAMPLE 3

Tablet Formulation

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Present compound)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

EXAMPLE 4

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of the present compound in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A method of modulating a cannabinoid receptor which comprises administering to a subject in need thereof, an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

2. A method of treating an immunologically-mediated inflammatory disease selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple sclerosis, diabetes and thyroiditis which comprises administering to a subject in need thereof an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

3. A method of treating a disease selected from the group consisting of ankylosing spondylitis, gout, gouty arthritis, osteoarthritis and osteoporosis which comprises administering to a subject in need thereof an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

4. A method of treating renal ischemia which comprises administering to a subject in need thereof an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

5. A method of treating brain trauma due to edema resulting from cranial injury which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24803

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/045
US CL :514/729

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/729

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, HCAPLUS, USPATFULL- compound of claims for any therapeutic purpose.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ONG, S.H. Adamantyl-substituted phenols. J. Chem. Soc. D. 1970, Vol. 18, page 1180.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 JANUARY 1999	Date of mailing of the international search report 26 FEB 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer M. MOEZIE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*